PATENT SPECIFICATION

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COMPLETE SPECIFICATION

NO DRAWINGS

Improvements in Novel Otologic Preparations and the Process for Their Preparation

We, MUNDIPHARMA, A.G., a corporation organized and existing under the laws of Switzerland, of Bahnhofstrasse 41, Aarau, Switzerland; do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with therapeutic preparations intended for use in the ear in order to treat otologic disease as well as to soften and remove the waxy exudate (cerumen) found in the ear canal. In particular, the invention describes the use of a special surface-active agent which may also be mixed with a hydroscopic aqueous-miscible solvent, not irritating to the ear, which serves to soften and remove the cerumen and debris of the ear canal and as a vehicle for otologic medicaments. A further object of the invention is to provide processes for the preparation of the materials described.

A vehicle or carrier of medication intended for use in the ear must meet requirements not shared by a carrier of medication for internal use (whether orally or by injection) or even topical preparations intended for use on skin in dermatologic practice. An otologic vehicle, in addition to acting as a carrier or reservoir of therapeutic agents, should protect the sensitive tissues of the ear canal, facilitate the removal of cutaneous secretions and exudates, and influence the penetration of the drug into the surrounding tissues. The more important physico-chemical properties of such materials are concerned with their volatility, viscosity, aqueous solubility and miscibility and their compatibility with therapeutic agents.

It is desirable that such a preparation be non-volatile and have a viscosity of not less than 40 centipoises at 20°C, and of course that it be non-toxic to the ear. Also vehicle and therapeutic agent must be compatible. The hygroscopic properties of the mixture are very important since aqueous transudates are found in the ear canal which must be absorbed without interfering with the critical values of the viscosity and volatility. Aqueous miscibility is an adjunct to the facilitation of the absorption of exudates as well as the transferral of therapeutic materials. These latter properties broadly refer to the basic characteristics of this class of preparations, and the vehicle for use in the ear must, in addition, have the function of both softening and removing the ear-wax (cerumen).

Cerumen is a peculiar and unique exudate of both the normal and diseased ear canal which actively inhibits and interferes with the action of medications, as well as giving rise to active aural symptomatology which may be disturbing and painful to the patient and hence it must be removed preliminary to the effective application of therapeutic agents into the ear. Cerumen markedly reduces the effectiveness of germicidal and antiseptic substances in the ear as well as acting to support the growth of certain micro-organisms. Itching, pain, a sense of fullness, noises and even deafness may result from impacted cerumen. Occlusion of the ear drum may occur quite suddenly by water entering the ear canal causing the wax to swell. This is frequently the case in individuals who submerge their heads in water during bathing, and tinnitus and even vertigo has been known to result because of the pressure against the ear drum.

Removal of the impacted cerumen is necessary to relieve the symptoms. This procedure is often a difficult one and in instances where the wax has accumulated

over a period of time, has required mechanical or surgical manipulation for its disintegration and consequent removal. The prophylactic value of the removal of hardened ear wax has been pointed out by many investigators and is frequently the cause of common otologic complaints since the accumulation of the debris and wax in the ear canal macerates and irritates the tissue making it more susceptible to disease. It has been shown that external otitis and eczematous lesions of the external ear are frequently related to ear wax accumulation.

The method of removing ear wax or cerumen has been standardized to a very great extent. Syringing the ear and manual manipulation of the wax with a blunt-edged probe is the basic technique. It is advisable and necessary to soften the wax before it can be effectively removed. Frequently, where the cerumen has been impacted for a long time, the outer layer of the epithelium of the canal has become attached to it.

It has been noted that oily preparations used for softening purposes do not have any disintegrating effect on the ear wax. Failure has also been observed after the use of alkaline solutions such as the Sodium Carbonate Ear Drops of the British Pharmacopeia Codex and the Hydrogen Peroxide Ear Drops of the British Pharmacopeia Codex. The use of hygroscopic agents such as propylene glycol, glycerine and polyoxyethylene glycol have been found to swell the wax without disintegrating it, thereby increasing the hazards of pressure-reactions developing, as well as to cause them to be contraindicated for use in sensitive ears with impacted cerumen. This noxious action of the hygroscopic agent is completely eliminated by the present invention.

The most common procedures involve the use of pressure irrigation with either physiological saline solution or hypertonic saline solutions. A major disadvantage with a technique of this type is that it requires copious quantities of solution for irrigation purposes, and frequently necessitates special techniques for its administration and handling. Through the use of the present invention, ear wax may be effectively softened and disintegrated without the use of quantities of irrigating solutions or fluids and may be conveniently removed without injury to the delicate tissue of the ear canal.

Briefly, the present invention consists primarily in the use as a cerumenolytic agent of a protein-fatty acid condensate which is preferably mixed with a viscous hygroscopic aqueous miscible solvent such as propylene glycol, glycerine or polyoxyethylene glycol, to form a homogeneous, clear solution, which is substantially free of odor and stable under the ordinary conditions of storage. Chemically, the protein-fatty acid condensates are salts of N-acylated polypeptides of the following formula:

Alkyl-CO-HN-$(CHR\text{-}CO\text{-}NH)_n$-CHR-COOX

in which "Alkyl" denotes either a straight chain, or branched chain olefinic group consisting of from 8 to 20 carbons; "R" is a hydrogen atom or an alkyl group; the group "(CHR-CO-NH)" denotes the amino acid radicals (which may consist of a plurality of the same or various amino acid radicals in peptide linkage) forming the polypeptide residue; "n" stands for the number of peptide groups in the molecule, ranging from four to ten, while "X" stands for potassium, sodium, lithium or triethanolamine. Thus it is sufficient that the polypeptide residue may consist of from 4 to 10 peptide linkages, each of which consist of a plurality of amino acid radicals in peptide linkages. These agents are available commercially as "Maypon".

An aqueous solution of these preparations shows the well defined picture of colloids under the ultra-microscope and the repeated pattern of the CO-NH grouping is a strong source of protective-colloid characteristics having strong dispersing and emulsifying capacities. The hydration potential originating from the CO—NH grouping causes a high solubility of these substances and although they are only very slightly soluble in oil, they wet and penetrate less rapidly than most of the sulfated or sulfonated surface-active agents. Moreover, these agents lack the agressive tendencies and substantivities of the strongly dissociated detergents and consequently, do not cause skin to become extremely dry or hair to become brittle. These agents buffer alkali thereby protecting tissue against alkaline attacks, as well as protecting against other damaging agents such as thioglycollic acid and quaternary bases by their colloid nature without diminishing their own effective properties.

The protein-fatty acid condensates are weakly dissociated so that they may be compounded with cationic substances to form useful compositions. They are also compatible with certain anionic agents. In solution, these compounds are approximately neutral or slightly acid in pH, (pH 6 to pH 7.5), and are stable under the usual methods of storage.

A particular advantage of these compounds for use as a cerumenolytic agent is the similarity between the polypeptide chain of the compound and the protein composition of cerumen. The affinity between these substances provides a specific method of attack on the ear wax causing a more rapid and complete disintegration. The emulsifying properties of the compound then remove the debris without altering the physiology of the sensitive ear tissues.

When these agents are dissolved, in a viscous, hygroscopic solvent such as glycerine, polyoxyethylene glycol, or propylene glycol, the dehydrating properties of the combination as well as the aqueous miscibility of the mixture facilitate the emulsification in the cleansing process. The mixture is made viscous to provide a strong tenacious film of the substances in intimate contact with the surfaces of the ear canal to permit prolonged contact of the active therapeutic ingredient therewith.

Furthermore, when the combination of the N-acylated polypeptide and the polyhydroxy derivative is used as a vehicle with active ingredients intended to treat ear diseases, the resulting product possesses a degree of activity which is greater than that of the conventional aqueous solution or that of the viscous solvent. The reduced surface tension of the combination has a greater spreading power and thereby permits the drug to penetrate to and into the tissues easier and faster than does the conventional otologic preparation.

The following examples provide illustrations of the present invention.

Example 1

To one litre of propylene glycol, in a distillation flask, is added a concentrated aqueous solution of the triethanolamine salt of polypeptide fatty acid condensate (known commercially as "Maypon-4-CT") which contains at least 30 per cent of active solids so that the quantity of protein-fatty acids condensate is substantially 10% by weight of the total mixture when calculated on an anhydrous basis. The mixture is stirred and the flask is then fitted to a vacuum distillation apparatus and the water removed under 0.2 mm. Hg. pressure. Gentle warming may be used to facilitate the dehydration procedure, but this is not necessary under ordinary conditions. When the water content of the mixture is less than three per cent, the distillation is stopped and the mixture bottled into units to be used for further compounding as a vehicle for medications intended for the ear, or to be used directly to soften and remove ear wax.

The resultant product is a clear homogeneous mixture ranging in color from light yellow to amber with virtually no odor, but has the typical fatty taste of oleaginous materials. The mixture may be characterized physically by its specific gravity which ranges from 1.27 to 1.47; its viscosity which ranges from 40 to 120 centipoises. The pH of a ten per cent aqueous dilution is not less than pH 6.3 nor greater than pH 7.3. The product has a maximum residual ash content of 0.3 per cent and gives a positive biuret test.

Example 2

To one litre of polyoxyethylene glycol-200, in a round-bottom boiling flask, is added the concentrated aqueous solution of the lithium salt of the protein-fatty acid condensate, which is known in the trade as "Maypon 1101". The amount of concentrated aqueous solution of the surface active agent to be added depends upon the per cent active material which may range from 20 to 40 per cent, but should be sufficient to provide a final concentration of surface active agent in the polyoxyethylene glycol of ten per cent by weight when the water has been essentially removed. Thus, if a material with a concentration of 30 per cent active salt is used, approximately 333 grams of the concentrated aqueous material must be added to a litre of polyoxyethylene glycol-200 to provide a ten per cent concentration of the compound on an anhydrous basis.

After the addition of the protein condensate, the mixture is stirred to provide thorough mixing and the flask fitted to a vacuum still. The water is removed under reduced pressure (0.2 mm. Hg) until the constant weight. While it is possible to completely dehydrate the mixture, it is not necessary to do so for most purposes. A concentration of water below three per cent does not interfere with either the therapeutic activity of the mixture nor the stability of the preparation. When the mixture is hydrated so as to exceed 3% water, then the hygroscopic features of the solvent are impaired and the possibility of causing expansion of the mixture-cerumen mass is increased. After the proper level of dehydration has been achieved, the mixture may be packaged in units for use as a cerumenolytic agent or utilized for further compounding of therapeutic otologic preparations.

The solution obtained in this manner is a clear, homogeneous light yellow solution having a characteristic specific gravity of between 1.27 and 1.47 and a viscosity of between 40 and 100 centipoises, depending upon the amount of moisture in the same, and the viscosity of the polyoxymethylene glycol used as a starting substance.

Example 3

To ten pounds of anhydrous glycerin in a round-bottom boiling flask is added sufficient triethanolamine salt of the fatty acid-protein condensate known in the trade as "Maypon-4-CT", to provide a concentration of 15 per cent of the surface active agent, based upon the dry weight of the mixture. The mixture is stirred and the water evaporated under reduced pressure, (below 0.2 mm. Hg.), to constant weight or to a degree of hydration below three per cent. The dehydrated mixture may be bottled and used as an agent to soften and remove ear wax or utilized in the compounding of therapeutic preparations intended to treat ear disease.

Example 4

In place of the indicated salt of the fatty acid-protein condensate used in Examples 1, 2 or 3, there may be substituted either the lithium, potassium, sodium or triethanolamine salt of the compound described in the same equimolar concentrations. The optimal range of concentration for these compounds is between 7.5 and 20 per cent by weight based upon the anhydrous mixture. The fatty acids which are condensed with the polypeptide chain may consist preferably of lauric, palmitic, stearic or oleic acids. The aliphatic fatty acids of from eight to twelve carbons in chain length may also be used, but these are generally preferred for certain specialized purposes, as for example the undecylenic fatty acid-polypeptide condensate, which has the specific advantage of adding anti-fungal properties to the combination in addition to the surface activity and cerumenolytic characteristics.

Example 5

In place of either the propylene glycol or polyoxyethylene glycol-200 or the glycerin as used in Examples 1, 2 and 3, respectively, there may be substituted wholly, or in part, either polyoxyethylene glycol-400 or 600 or polyoxyethylene glycols having average molecular weights in the range 200 to 600. When these higher polyoxyethylene derivatives are used, the solution may tend to crystallize on standing, but this may be readily corrected with the aid of gentle heating prior to use.

Example 6

When the glycerine or propylene glycol or polyethylene glycol solution of the protein fatty-acid condensate is desired to be used as a solvent for medications intended to treat otologic disease, the desired therapeutic ingredient is dissolved in the mixture in the appropriate concentration with the aid of agitation or through gentle heat. A clear homogeneous solution results which is stable, pharmaceutically elegant and therapeutically active. Examples of the classes of medicaments which may be added to the solutions described above are:

CLASS	*SOME REPRESENTATIVE MEMBERS OF THIS CLASS*	*SUGGESTED CONCENTRATION OF THE SUBSTANCE PER CC*
Antibiotics	Polymyxin-B-Sulfate	10,000 units
	Neomycin	5 mgm.
	Aureomycin	5 mg.
	Tetracycline	50 mg.
	"Chloromycetin" (Regd. Trade Mark)	0.5 %
	"Terramycin" (Regd. Trade Mark)	5 mgm.
	Bacitracin	200 units
	Erythromycin glucoheptonate	25 mg.
	Dihydrostreptomycin	1.5 mg.
	Tyrothricin	0.05 %
Antiseptics	Sulfanilamide	5 %
	Sulfathiazole	5 %
	Sulfisoxazole	5 %
	Sulfacetimide	5 %
	Sodium propionate	1-3 %
	Chlorobutanol	0.5 %
	Hydrogen peroxide	3.0 %
	Orthohydroxyphenylmercuric Chloride	0.05 %
	Phenol	1-3 %
	Benzethonium chloride	5 %
Anesthetics	Benzocaine	2-4 %
	Procaine butyrate	3-4 %
	Eucupin	2-4 %
Anti-inflammatory Agents	Hydrocortone	10 mg.
	Pregnenolone	1 mg.
	Glycyrrhetinic Acid	2-5 %
	Antipyrine	3-5 %
Astringents	Tannic Acid	5 %
	Zinc Sulfate	1-2 %
	Aluminum Acetate	5-10 %
Antihistaminics	Phenyltoloxamine citrate	10 %
	Chloroprophenpyridamine Maleate	1 %

Procedures employed in softening and removing ear wax are varied but essentially they call for manual removal after softening, either by swabbing, irrigating or removal with an instrument. In order to amplify and enhance the action of the condensates, the condensate or the mixture is introduced into the ear canal by dropper or other conventional means, in the case of the mixture the condensate being preferably in the 10 to 15% concentration. However, it should be noted that very fine results may be obtained when the protein-fatty acid condensate consists of 7½ to 20% of the dry weight of the mixture. The minimum figure of 7½% is particularly significant since below such concentration the ability of the compound to lower surface tension is so seriously impaired as to render the mixture impractical. The upper figure of 20% is not a maximum critical figure. The significance of the 20% maximum however is that if the condensate proportion is increased beyond 20%, the wax softening action of the compound is not improved.

After a period of time has elapsed to enable the exercise of the softening effect upon the ear wax (for example, 15 minutes) the wax is then removed, the favorite means thus far being that of general irrigation. Under some conditions such as those found in various types of draining ears, it is not necessary to utilize a water wash to remove the disintegrated ear wax and this material may be eliminated through draining, such drainage being comprehended by the term "mechanical removal" as said term is used in the claims herein.

It is not desired to be limited except as set forth in the following claims, the above description being by way of illustration of the invention.

WHAT WE CLAIM IS:—

1. A cerumenolytic agent characterized by comprising a hygroscopic aqueous-miscible solvent which is non-toxic to the ear and a protein-fatty acid condensate in the form of a salt of N-acylated polypeptides of the formula

Alkyl-CO-HN-(CHR-CO-NH)$_n$-CHR-COOX

in which "Alkyl" consists of an aliphatic fatty acid radical having from 8 to 20 carbons, "R" is a hydrogen atom or an alkyl group, the group "(CH-CO-NH)" represents an amino acid radical in peptide linkage forming a polypeptide residue, "n" is equal to the number of peptide groups in the molecule which may extend over the range 4 to 10 inclusive and "X" represents potassium, sodium, lithium or triethanolamine.

2. A cerumenolytic agent according to claim 1, characterized in that said solvent is glycerine, propylene glycol or polyoxyethylene glycol having a molecular weight within the range of 200 to 600.

3. A cerumenolytic agent according to claim 1 or 2, characterized in that it further comprises a compatible therapeutic ingredient.

4. A cerumenolytic agent according to any one of claims 1 to 3, characterized by being dehydrated.

5. A method for preparing a cerumenolytic agent, characterized by mixing a protein-fatty acid condensate in the form of a salt of N-acylated polypeptides of the formula

Alkyl-CO-HN-(CHR-CO-NH)$_n$-CHR-COOX

in which "Alkyl" consists of an aliphatic fatty acid radical having from 8 to 20 carbons, "R" is a hydrogen atom or an alkyl group, the group "(CHR-CO-NH)" represents an amino acid radical in peptide linkage forming a polypeptide residue, "n" is equal to the number of peptide groups in the molecule which may extend over the range 4 to 10 inclusive and "X" represents potassium, sodium, lithium or triethanolamine, with a hygroscopic aqueous-miscible solvent which is non-toxic to the ear.

6. A method according to claim 5, characterized in that said solvent is glycerine, propylene glycol or polyoxyethylene glycol having a molecular weight within the range of 200 to 600.

7. A method according to claim 6, characterized in that said protein-fatty acid condensate is added in a proportion of at least 7½% by weight of the dry weight of the mixture.

8. A method according to claim 6 or 7, characterized in that a compatible therapeutic ingredient is added to said cerumenolytic agent.

9. A method according to any one of claims 6 to 8, characterized in that said cerumenolytic agent is dehydrated.

10. A method according to claim 9, characterized in that said dehydration comprises the step of evaporating under reduced pressure the water from said cerumenolytic agent to a degree of hydration below 3%.

11. A method for preparing a cerumenolytic agent by mixing a protein-fatty acid condensate with a hygroscopic solvent substantially as described.

12. A cerumenolytic agent substantially as described.

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